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Associations between benign cutaneous nevi and risk of Type 2 diabetes mellitus in men and women: results from two prospective cohort studies

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Abstract

Aim—To examine the association of cutaneous nevi with Type 2 diabetes risk.

Methods—We prospectively examined the associations between nevus count and risk of Type 2 diabetes among 26 240 men (1988–2010) from the Health Professionals Follow-up Study and 67 050 women (1986–2010) from the Nurses' Health Study. Information on the numbers of cutaneous

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Competing interests

None declared.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1 Hazard ratios and 95% CIs for Type 2 diabetes according to the number of cutaneous nevi (seven categories).

nevi on arms at baseline and incident cases of Type 2 diabetes was collected using validated questionnaires.

Results—During 1 879 287 person-years of follow-up, we documented 9040 incident cases of Type 2 diabetes. After adjustment for age, BMI and other diabetes risk factors, greater number of nevi was associated with higher risk of Type 2 diabetes. Multivariable-adjusted hazard ratios for <1, 1–5, 6–14 and ≥15 nevi were 1.00 (reference), 1.02 (95% CI 0.93, 1.13), 1.08 (95% CI 0.88, 1.34) and 1.57 (95% CI 1.15, 2.15), respectively, for men (*P* for linear trend = 0.01), and 1.00 (reference), 1.07 (95% CI 1.02, 1.13), 0.98 (95% CI 0.87, 1.10), and 1.25 (1.01, 1.54), respectively, for women (*P* for linear trend = 0.05). This positive association remained consistent across subgroups stratified by age, BMI, multivitamin use, smoking status, alcohol, physical activity, history of hypercholesterolaemia, family history of diabetes, history of hypertension and menopausal status (in women).

Conclusions—Cutaneous nevus count may represent a novel marker for development of Type 2 diabetes, suggesting a possible unique melanocytic nevus-related mechanism in the pathogenesis of Type 2 diabetes. Further studies are warranted to confirm the findings and to investigate the underlying mechanisms.

Introduction

Melanocytic nevi are risk markers and potential precursors for melanoma [1,2]. Nevi are more common among those with fair skin, sun sensitivity and freckling, and their development is influenced by age, sex and sun exposure [3]. Recent studies have suggested that the number of cutaneous nevi may reflect endogenous hormone imbalances, which could be an important risk factor for metabolic syndrome, which is related to Type 2 diabetes.

Two previous studies found that women with more nevi were more likely to be diagnosed with breast cancer than their counterparts who reported no nevi, which suggested the number of cutaneous nevi may reflect plasma sex hormone levels [4,5]. In addition, postmenopausal women with six or more nevi had significantly higher levels of free oestradiol and free testosterone than those with no nevi, indicating the potential utility of nevi as a marker of postmenopausal women's endogenous sex hormone levels. Cumulative evidence from observational studies has documented an association between endogenous hormones and risk of Type 2 diabetes mellitus. For instance, we found that circulating levels of oestradiol and testosterone were independently related to risk of Type 2 diabetes in both men and postmenopausal women [6]. Our previous findings also indicated significant sex differences for the associations between endogenous testosterone and Type 2 diabetes [7]; testosterone levels were positively associated with Type 2 diabetes risk among women but inversely related to Type 2 diabetes risk among men. With the onset of menopause and the concurrent decrease in oestrogen, Type 2 diabetes risk increases among postmenopausal women. High oestradiol levels may be associated with high risk of diabetes in both women and men [7,8]. In addition, other endogenous peptide hormones, such as α -melanocyte-stimulating hormone (α -MSH), leptin and insulin-like growth factor (IGF), may also be involved in both neviogenesis and glucose homeostasis [9,10].

Given the intriguing findings linking cutaneous nevus count to endogenous hormone levels, we hypothesize that nevus count may be a novel phenotypic marker of Type 2 diabetes. We prospectively investigated, therefore, whether and to what extent the number of cutaneous nevi is related to risk of Type 2 diabetes in men and women, based on two large well-characterized cohort studies, the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NuHSt).

Methods

Study population

Study participants were those included in two on-going prospective cohort studies: the HPFS and the Nurses' Health Study. In brief, the HPFS was established in 1986 when 51 529 male health professionals aged 40–75 years answered a detailed questionnaire that included a comprehensive diet survey and items on lifestyle practice and medical history. The Nurses' Health Study was established in 1976 when 121 701 female registered nurses aged 30–55 years living in the USA were enrolled using a mailed questionnaire that included questions about their medical histories and lifestyle practices. Details of these cohorts have been described previously [11,12]. Information on lifestyle factors and medical histories was collected biennially via mailed questionnaires, and updated biennially. Responses to questions about nevus count were only collected once. The follow-up rates exceed 90% in both studies.

For the present investigation, we used 1986 for the Nurses' Health Study and 1988 for the HPFS, when we first obtained detailed information on the number of cutaneous nevi, as our baseline years. We excluded participants with a history of diabetes (Type 1 or Type 2 diabetes), and those with missing date of birth, cardiovascular disease or cancer. The final study population consisted of 26 240 men from the HPFS and 67 050 women from the Nurses' Health Study.

The study protocol was approved by the institutional review board of the Brigham and Women's Hospital and the Human Subjects Committee Review Board of the Harvard School of Public Health. All the participants provided informed consent.

Assessment of exposure

Data on number of cutaneous nevi were collected in the baseline questionnaire for each cohort. Participants reported numbers of cutaneous nevi that were ≥ 3 mm in diameter at baseline on their left arm, from shoulder to wrist, using the categories of 0, 1–2, 3–5, 6–9, 10–14, 15–20 and > 20 .

Identification of Type 2 diabetes

The primary endpoint for this study was incident Type 2 diabetes. On the biennial questionnaires, participants responded to a question on physician-diagnosed Type 2 diabetes. For those reporting diabetes, a supplementary questionnaire was then sent for confirmation of the report and ascertainment of the date of diagnosis. Cases of Type 2 diabetes were defined as initially self-reported diabetes subsequently confirmed by the validated

questionnaire [13,14]. Cases before 1998 were diagnosed using criteria consistent with those proposed by the National Diabetes Data Group [15]. Cases during the 1998 and 2002 cycles were diagnosed using the American Diabetes Association's diagnostic criteria [16]. These criteria were the same as those proposed by the National Diabetes Data Group except for the elevated fasting plasma glucose criterion, for which the threshold was changed from 7.8 mmol/L (140 mg/dL) to 7.0 mmol/L (126 mg/dL). The diagnosis was confirmed in the study if at least one of the criteria above was met.

The validity of the supplementary questionnaire has been established in two previous studies in the Nurses' Health Study and the HPFS through medical record reviews. In both studies, diagnosis of Type 2 diabetes was confirmed in >97% of the cases [14,17].

Assessment of covariates

Data on risk factors for Type 2 diabetes were obtained from questionnaires in both cohorts in the 1980s [18,19]. These risk factors included age, ethnicity, BMI, exercise, menopausal status and postmenopausal hormone usage, total energy intake, alcohol intake, smoking, hypertension, hypercholesterolaemia and family history of diabetes, multivitamin intake and dietary intakes of polyunsaturated fat, saturated fat, trans fat, magnesium, glycaemic load, caffeine and cereal fibre. In the biennial follow-up questionnaires, we updated information on a participant's age, weight, smoking status, physical activity, menopausal status and use of postmenopausal hormone therapy (for women), oral contraceptive use (for women), and personal history of chronic diseases. Height was ascertained on the 1976 enrolment questionnaire in the Nurses' Health Study and the 1986 enrolment questionnaire in the HPFS. We calculated BMI as weight in kilograms divided by height in metres squared. Self-reports of body weight have been shown to be highly correlated with measured weights ($r=0.96$) in the Nurses' Health Study and the HPFS [20]. The presence or absence of a family history of diabetes (in first-degree relatives) was assessed in 1982 and 1988 in the Nurses' Health Study and in 1987 in the HPFS. Information on intakes of alcohol and other beverages was updated every 4 years using the food-frequency questionnaire. These covariates were predetermined before data analysis as they were well-established risk factors for Type 2 diabetes or significant predictors of Type 2 diabetes from previous diabetes studies in these two cohorts.

Statistical analysis

We calculated person-years of follow-up for each participant from the return date of baseline questionnaire (1986 for the Nurses' Health Study and 1988 for the HPFS) to the date of diagnosis of Type 2 diabetes, death, date of loss to follow-up, or the cut-off date (30 June 2010 in the Nurses' Health Study and the HPFS), whichever came first. Based on the categorical information from the questionnaire, we grouped women into four categories according to number of cutaneous nevi, 0, 1–5, 6–14 and ≥ 15 nevi, and compared each of the last three groups with the group reporting no nevi. Risks of incident Type 2 diabetes were calculated according to the number of cutaneous nevi in the HPFS and Nurses' Health Study, separately. In the age-standardized analysis of basic characteristics, P values for overall comparison among four groups of number of nevi for HPFS and Nurses' Health Study were calculated from age-adjusted linear regression analysis for each continuous

variable and age-adjusted logistic regression analysis for each categorical variable, respectively. We only used baseline covariates for regression adjustment because the secondary analyses of repeated measurements of most covariates had a relatively high correlation between their baseline measurements and the respective follow-up measurements in these two cohorts.

We used Cox proportional hazard models to calculate hazard ratios (HRs) and 95% CIs for Type 2 diabetes according to the number of cutaneous nevi in the two cohorts, separately. The combined HRs were calculated by pooling the HRs obtained for the HPFS and Nurses' Health Study using a DerSimonian and Laird random-effects meta-analysis model. To test for a linear trend, we modelled the number of cutaneous nevi as a continuous variable by assigning the median nevus count value of each category and the lower bound of the top category. The *P* values for linear trends in both cohorts were calculated using the trend estimation method [21]. Tests for interaction by sex (or cohort) were performed using the Wald test for the cross product interaction term. Stratification analysis was performed by age (< 65 years and ≥ 65 years), multivitamin use (current, never and past), smoking status (current, never and past), BMI (normal weight, BMI < 25 kg/m²; overweight, BMI 25.0–29.9 kg/m²; and obese, BMI ≥ 30.0 kg/m²), alcohol (never/rarely, at least once a month), physical activity (< 1000 kcal/w and ≥ 1000 kcal/w), history of hypercholesterolaemia (No or Yes), family history of diabetes (No or Yes), and history of hypertension (No or Yes) in the two cohorts. Menopausal status (premenopausal and postmenopausal) was additionally stratified in the Nurses' Health Study. Formal tests for interactions by these factors were also performed using the Wald test for the cross product interaction term.

In multivariable Cox regression models, we adjusted for age (1-year increment), smoking status [never, past, current (1–14, 15–24, and 25+ cigarettes/day)], alcohol consumption (never, 0.1–4.9 g/day, 5–29.9 g/day, and ≥ 30 g/day), exercise (<3 metabolic equivalents of task (MET)/week, 3–9 MET/week, 9–18 MET/week, 18–27 MET/week, and ≥ 27 MET/week), ethnicity (white and others), BMI (0–22.9, <23, 23–24.9, 25–29.9, 30–34.9 and ≥ 35 kg/m²), hypertension, hypercholesterolaemia, family history of diabetes, multivitamin intake, calorie intake (quintiles), ratio of polyunsaturated to saturated fat (quintiles), trans fat (quintiles), magnesium (quintiles), cereal fibre (quintiles), caffeine (quintiles), and glycaemic load (quintiles). The Nurses' Health Study cohort was additionally adjusted for menopausal status (premenopausal and postmenopausal) and postmenopausal hormone usage (never, past and current). An indicator was created for the missing data for each covariate. To assess the proportionality assumption, we created interactive terms for the main predictors and time to event (nevi×time) in the larger model, and compared the smaller model, without any time-dependent main predictors, with the larger model that included all of the time-dependent main predictors. The test was carried out by a Wald statistic with one degree of freedom and chi-squared distribution under the null hypothesis.

All statistical analyses were conducted using the SAS software (version 9.3; SAS Institute, Cary, NC, USA). All statistical tests were two-tailed, and the significance level was set at *P* < 0.05.

Results

During 1 879 287 person-years of follow-up, we documented 9040 incident cases of Type 2 diabetes in both cohorts. In Table 1, we presented age-standardized baseline characteristics of study participants according to the number of cutaneous nevi among 26 240 men in the HPFS (1988) and 67 050 women in the Nurses' Health Study (1986). Participants with more cutaneous nevi were more likely to have a higher BMI, frequently use multivitamins, to have a history of hypertension and hypercholesterolaemia and family history of diabetes, and to consume more calories, high glycaemic load food, more magnesium and less cereal fibre than those with no nevi. Current smokers and heavier female alcohol consumers tended to have fewer cutaneous nevi. In addition, men with more cutaneous nevi were physically less active. Women with more cutaneous nevi were more likely to be premenopausal, to use more hormone therapy among postmenopausal women, and to consume more fat.

Women and men with more cutaneous nevi had a significantly greater risk of developing subsequent Type 2 diabetes (Table 2 and Table S1). Compared with individuals with no nevi, the age-adjusted HRs (95% CIs) for 1–5 nevi, 6–14 nevi, and ≥15 nevi were 1.09 (95% CI 0.99, 1.20), 1.20 (95% CI 0.97, 1.48), 2.00 (95% CI 1.47, 2.72), respectively, for men (*P* for linear trend < 0.0001) and 1.15 (95% CI 1.09, 1.21), 1.25 (95% CI 1.11, 1.40), 1.70 (95% CI 1.38, 2.09), respectively, for women (*P* for linear trend < 0.0001). After adjustment for age, ethnicity, BMI, physical activity, total energy intake, alcohol intake, smoking, menopausal status and postmenopausal hormone usage (women), hypertension, hypercholesterolaemia and family history of diabetes, multivitamin intake and dietary intake, the associations remained statistically significant among women and men, respectively (Table 2). Compared with individuals with no nevi, the multivariable-adjusted HRs (95% CIs) for 1–5 nevi, 6–14 nevi, and ≥15 nevi were 1.02 (95% CI 0.93, 1.13), 1.08 (95% CI 0.88, 1.34) and 1.57 (95% CI 1.15, 2.15) for men (*P* for linear trend = 0.01), and 1.07 (95% CI 1.02, 1.13), 0.98 (95% CI 0.87, 1.10) and 1.25 (95% CI 1.01, 1.54) for women (*P* for linear trend = 0.05), respectively. In the meta-analysis of the results from both men and women, the multivariable-adjusted HRs (95% CIs) of Type 2 diabetes for those with 1–5 nevi, 6–14 nevi, and ≥15 nevi were 1.06 (95% CI 1.01, 1.11), 1.00 (95% CI 0.91, 1.11) and 1.36 (95% CI 1.10, 1.69) as compared with those with no nevi (*P* for linear trend = 0.005). There was no significant between-study heterogeneity for summary results from each cohort (*P* = 0.430, *I*² = 0.0% for those with 1–5 nevi; *P* = 0.394, *I*² = 0.0% for those with 6–14 nevi; *P* = 0.429, *I*² = 28.7% for those with ≥15 nevi; *P* = 0.236).

We also examined whether the observed associations were modified by major Type 2 diabetes risk factors, including age, multivitamin use, menopausal status, smoking status, BMI, alcohol intake, physical activity, history of hypercholesterolaemia, family history of diabetes and history of hypertension. None of them significantly modified the association between the number of cutaneous nevi and Type 2 diabetes (Tables 3 and 4).

Discussion

In the present study, we found that mole count on participants' arms at baseline was significantly associated with increased risk of Type 2 diabetes among men and women. This

association remained significant after adjusting for previously known risk factors for Type 2 diabetes and was consistent across subgroups of participants. To our knowledge, the present study is the first to prospectively examine the association of melanocytic nevus count with Type 2 diabetes risk. Our results indicate a potential common mechanism shared by nevogenesis and Type 2 diabetes, although further studies are warranted to confirm our findings and clarify the underlying mechanism.

The positive association between nevus count and Type 2 diabetes risk may be partly attributable to shared risk factors between the trait and the disease. First, endogenous sex steroid hormones may play an important role in the pathogenesis of both moles and Type 2 diabetes. There are several pieces of evidence supporting the possible link. For example, nevi typically darken and enlarge during pregnancy. This observation suggests that altered balance of endogenous hormonal status may influence nevogenesis and that the numbers of nevi could possibly reflect an individual's levels of endogenous hormones. Plasma levels of testosterone, sex hormone-binding globulin and oestradiol with risk of Type 2 diabetes have been systematically examined by our previous meta-analysis [7], which suggested that endogenous sex hormones could differentially modulate glycaemic status and risk of Type 2 diabetes in men and women.

In a cross-sectional study of 611 postmenopausal women without postmenopausal hormone use from the same Nurses' Health Study cohort, those with six or more nevi had a 45.5% higher level of free oestradiol and a 47.4% higher level of free testosterone than those without nevi [5], indicating the potential utility of number of nevi as a marker of postmenopausal women's endogenous oestrogen and testosterone levels.

Second, several possible factors, including endogenous peptide hormones, α -MSH, leptin, and IGF-1, might also explain the link between nevogenesis and Type 2 diabetes. Emerging experimental evidence suggests that α -MSH can stimulate melanogenesis and increase insulin sensitivity when present in the central nervous system or periphery [22]. Leptin produced by adipose tissue regulates various obesity or Type 2 diabetes-related physiological pathways, including appetite, body weight, neuroendocrine functions and glycaemia. Leptin has recently been linked with increased risk of melanoma. Melanocytes express leptin and leptin receptor, while nevi express high levels of leptin and low levels of leptin receptor [23]. Leptin may also serve as α -MSH antagonists, which leads to a lower activity of circulating α -MSH and melanocortin receptors [24]. IGF-1 is a growth factor produced primarily by the liver, and has important actions on glucose and insulin metabolisms. IGF-mediated kinases expressed in significant amounts in both benign and malignant melanocytes, such as IGF-1-R, are likely to play a role in melanoma genesis and progression [9]; however, evidence from population studies has yet to be described to support these mechanisms linking mole count and Type 2 diabetes.

The present study has several strengths. First, our findings were based on two large prospective cohort studies with large sample sizes and long follow-up durations, providing sufficient power for robust evidence. Second, we used self-reported information on moles and diagnosis as Type 2 diabetes. Although the 'gold standard' measure is clinical assessment by dermatologists, previous studies have found that self-assessment of nevi was

quite comparable to counts derived from clinical examinations [25,26]. The underascertainment and misclassification of Type 2 diabetes outcome are possible because the incident cases were self-reported physician-diagnosed diabetes; however, our validity studies indicated that self-reported diabetes was highly reliable in both male and female health professionals. Diabetes misclassification was likely to be non-differential and therefore will attenuate the associations toward the null. Third, we did not collect information on the number of moles on other body parts besides the left arm or on the type of moles, which may have led to residual confounding. Several studies have indicated, however, that measuring nevus count on the arms is a good predictor of full body nevus count [27,28]. Although distinct subsets of nevi may exist in the population, in the present study we focused only on common moles. Fourth, the numbers of cutaneous nevi may be age-dependent and changed by time [29]. We only collected baseline information on moles at the time each cohort was established; however, increased frequency of growing nevi was thought to be related to the growth hormone-rich environment in two periods (adolescence and pregnancy) [29], therefore, the number of nevi would be in the same classified group because most of our participants were postmenopausal women and adult men. Fifth, given that the multivariable-adjusted HRs were significant only for the largest category vs the lowest category, the trend test results should be interpreted with caution. Finally, we included only baseline covariates in the main analysis and ignored longitudinal information. Even though our secondary analyses of repeated measurements of most covariates showed a relatively high correlation between baseline measurements and the respective follow-up measurements in these two cohorts, time-varying confounding cannot be completely excluded.

In summary, the present prospective investigation, conducted in two large cohorts of US men and women, showed that number of nevi was significantly and positively associated with risk of Type 2 diabetes. This positive association remained significant after adjusting for previously known risk factors of Type 2 diabetes and was consistent across subgroups of participants. Our findings suggest that mole count could be a novel marker for development of Type 2 diabetes, indicating a unique nevus development-related mechanism. Further studies are warranted to confirm findings from the present study and investigate underlying mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new?

- Based on our previous findings on the association between endogenous sex hormone biomarkers and Type 2 diabetes mellitus, we first postulate a hypothesis that melanocytic nevus count may be a phenotypic marker of Type 2 diabetes risk via its link with sex steroid hormones.
- We prospectively investigated whether and to what extent the number of cutaneous nevi is related to risk of Type 2 diabetes in both men and women, based on two large well-characterized cohort studies, the Health Professionals Follow-up Study and the Nurses' Health Study.
- We found the number of nevi was significantly and positively associated with risk of Type 2 diabetes in both men and women.
- Our findings suggest that mole count could be a novel predictor for risk of Type 2 diabetes, independently of known diabetes risk factors.

Table 1

Age-adjusted baseline characteristics according to self-reported number of cutaneous nevi among participants in the Nurses' Health Study and the Health Professionals Follow-up Study*

Characteristic	Nurses' Health Study (women)						HPFS (men)					
	Number of cutaneous nevi						Number of cutaneous nevi					
	0 N=42648	1-5 N=21400	6-14 N=2436	15 N=566	P	0 N=17834	1-5 N=7060	6-14 N=1055	15 N=291	P		
Age [†] , years	52.8 (7.2)	52.1 (7.1)	51.9 (7.0)	51.9 (7.0)	<0.0001	54.5 (9.4)	54.7 (9.4)	55.8 (9.5)	56.4 (9.4)	<0.0001		
White, %	97	99	99	98	<0.0001	95	96	98	98	<0.0001		
BMI at age 18 years, kg/m ²	24.9 (4.5)	25.3 (4.7)	26.1 (5.1)	26.3 (5.2)	<0.0001	25.3 (3.0)	25.4 (3.1)	25.7 (3.3)	26.2 (3.5)	<0.0001		
Physical activity, MET h/week	14.4 (21.2)	14.3 (21.3)	14.0 (19.1)	15.2 (27.4)	0.60	29.7 (34.0)	27.9 (32.5)	26.3 (27.1)	26.0 (27.5)	<0.0001		
Alcohol consumption, g/day	6.4 (11.0)	6.2 (10.5)	6.2 (10.2)	5.4 (8.9)	0.03	12.2 (16.2)	12.1 (16.0)	12.0 (16.2)	12.6 (17.6)	0.91		
Past smokers, %	34	35	36	41	<0.0001	42	42	42	44	<0.0001		
Current smokers, %	22	20	20	19	<0.0001	9	8	7	9	<0.0001		
Multivitamin use, %	43	43	42	46	<0.0001	41	43	44	44	<0.0001		
Postmenopausal, %	54	54	53	52	<0.0001	-	-	-	-	-		
Current hormone users among postmenopausal women, %	27	28	31	30	<0.0001	-	-	-	-	-		
Hypertension, %	21	23	28	28	<0.0001	20	22	24	24	<0.0001		
Hypercholesterolemia, %	10	11	14	12	<0.0001	18	20	23	20	<0.0001		
Family history of diabetes, %	28	28	29	34	<0.0001	22	23	22	25	<0.0001		
Calorie intake, kcal/day	1749 (522)	1799 (529)	1824 (542)	1787 (568)	<0.0001	2009 (617)	2041 (620)	2039 (620)	2025 (619)	0.003		
Polysaturated fat, % from calories	6.1 (1.6)	6.2 (1.6)	6.2 (1.7)	6.2 (1.7)	0.005	5.9 (1.6)	5.9 (1.5)	6.0 (1.6)	5.9 (1.6)	0.77		
Saturated fat, % from calories	11.7 (2.6)	11.7 (2.5)	11.7 (2.6)	11.9 (2.9)	0.01	11.0 (2.8)	11.0 (2.7)	11.1 (2.8)	11.0 (2.6)	0.76		
Trans fat, % from calories	1.7 (0.5)	1.7 (0.5)	1.7 (0.5)	1.7 (0.5)	0.001	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.2 (0.5)	0.14		
Cereal fibre, g/day	4.8 (3.4)	5.0 (3.8)	5.0 (3.5)	4.8 (3.0)	<0.0001	5.9 (4.0)	6.0 (4.4)	6.2 (4.5)	5.7 (3.6)	0.02		
Glycaemic load	109.2 (40.7)	112.3 (41.2)	113.3 (42.1)	108.9 (42.3)	<0.0001	125.3 (47.8)	127.5 (47.8)	127.4 (47.6)	126.1 (47.0)	0.01		
Magnesium, mg/day	318.4 (105.2)	325.9 (106.4)	331.3 (108.3)	335.5 (112.9)	<0.0001	350.3 (119.1)	356.3 (120.3)	355.7 (125.1)	361.2 (135.7)	0.002		
Caffeine, g/day	295.3 (228.9)	295.3 (227.9)	294.2 (227.7)	308.7 (241.2)	0.70	232.9 (228.4)	226.6 (226.5)	231.9 (233.1)	262.2 (247.9)	0.12		

HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent of task.

Values are mean (SD), unless otherwise indicated, and are standardized to the age distribution of the study population.
* Based on information collected in the 1986 (Nurses' Health Study) and 1988 (HPFS) questionnaire unless specified otherwise.
[†]Value is not age-adjusted.

Table 2
Hazard ratios and 95% CIs for Type 2 diabetes, according to number of cutaneous nevi

Number of cutaneous nevi	Cases	Person-years	Age-adjusted HR (95% CI) [*]	Multivariable-adjusted HR (95% CI) [†]
Nurses' Health Study [‡]				
0	4198	886745	1.00	1.00
1–5	2419	446779	1.15 (1.09, 1.21)	1.07 (1.02, 1.13)
6–14	299	50670	1.25 (1.11, 1.40)	0.98 (0.87, 1.10)
15	90	11428	1.70 (1.38, 2.09)	1.25 (1.01, 1.54)
<i>P</i> for trend			<0.0001	0.05
HPFS				
0	1324	329181	1.00	1.00
1–5	575	130408	1.09 (0.99, 1.20)	1.02 (0.93, 1.13)
6–14	93	18982	1.20 (0.97, 1.48)	1.08 (0.88, 1.34)
15	42	5094	2.00 (1.47, 2.72)	1.57 (1.15, 2.15)
<i>P</i> for trend			<0.0001	0.01
Combined				
0	5522	1215926	1.00	1
1–5	2994	577187	1.14 (1.09, 1.19)	1.06 (1.01, 1.11)
6–14	392	69652	1.24 (1.12, 1.37)	1.00 (0.91, 1.11)
15	132	16522	1.79 (1.51, 2.12)	1.36 (1.10, 1.69)
<i>P</i> for trend			<0.0001	0.005

HPFS, Health Professionals Follow-up Study; HR, hazard ratio.

^{*} Adjusted for age and ethnicity.

[†] Multivariable models were adjusted for age, ethnicity, BMI, physical activity, total energy intake, alcohol intake, smoking, hypertension, hypercholesterolaemia and family history of diabetes, multivitamin intake and dietary intake such as: polyunsaturated fat vs saturated fat, trans fat, magnesium, glycaemic load, caffeine, and cereal fibre.

[‡] Nurses' Health Study additionally adjusted for menopausal status and postmenopausal hormone usage.

Table 3

Hazard ratios and 95% CIs for diabetes risk according to number of cutaneous nevi in subgroup analyses stratified by predetermined factors among participants in the Nurses' Health Study*

Subgroup	Number of cutaneous nevi				P trend	P for interaction
	0	1–5	6–14	15		
Age						
< 65 years	1.00	0.99 (0.92, 1.07)	0.93 (0.78, 1.10)	1.42 (1.09, 1.85)	0.27	0.13
65 years	1.00	1.15 (1.07, 1.24)	1.04 (0.88, 1.23)	1.00 (0.71, 1.42)	0.10	
Multivitamin use						
Current	1.00	1.08 (1.01, 1.15)	0.94 (0.80, 1.11)	1.03 (0.76, 1.38)	0.73	0.16
Never	1.00	1.08 (0.98, 1.19)	1.10 (0.90, 1.35)	1.47 (0.99, 2.19)	0.03	
Past	1.00	1.06 (0.93, 1.20)	0.82 (0.60, 1.14)	1.74 (1.09, 2.77)	0.30	
Menopausal status						
Premenopausal	1.00	1.03 (0.86, 1.23)	0.92 (0.63, 1.33)	0.89 (0.42, 1.90)	0.70	0.89
Postmenopausal	1.00	1.06 (1.01, 1.12)	0.98 (0.86, 1.11)	1.25 (0.99, 1.58)	0.09	
Smoking status						
Current	1.00	1.00 (0.86, 1.18)	0.89 (0.60, 1.31)	1.37 (0.72, 2.60)	0.79	0.38
Never	1.00	1.11 (1.03, 1.19)	0.87 (0.73, 1.05)	1.17 (0.83, 1.64)	0.21	
Past	1.00	1.05 (0.97, 1.13)	1.12 (0.95, 1.33)	1.30 (0.97, 1.75)	0.02	
BMI, kg/m ²						
Normal weight	1.00	1.05 (0.91, 1.20)	1.11 (0.78, 1.58)	0.90 (0.40, 2.02)	0.65	0.37
Overweight	1.00	1.15 (1.05, 1.25)	1.06 (0.86, 1.32)	1.50 (1.03, 2.18)	0.01	
Obese	1.00	1.03 (0.96, 1.10)	0.88 (0.76, 1.03)	1.12 (0.86, 1.47)	0.84	
Alcohol						
Never/rarely	1.00	1.05 (0.97, 1.12)	0.94 (0.79, 1.11)	1.05 (0.77, 1.43)	0.92	0.10

Subgroup	Number of cutaneous nevi				<i>P</i> trend	<i>P</i> for interaction
	0	1–5	6–14	15		
At least once a month	1.00	1.12 (1.04, 1.20)	1.03 (0.87, 1.23)	1.57 (1.17, 2.10)	0.003	
Physical activity						
1000 kcal/week	1.00	1.10 (1.02, 1.17)	1.00 (0.85, 1.17)	1.29 (0.98, 1.70)	0.05	0.85
>1000 kcal/week	1.00	1.05 (0.97, 1.13)	0.97 (0.82, 1.16)	1.26 (0.91, 1.74)	0.30	
History of hypercholesterolaemia						
No	1.00	1.11 (1.02, 1.20)	1.06 (0.87, 1.29)	1.30 (0.92, 1.86)	0.04	0.62
Yes	1.00	1.05 (0.98, 1.12)	0.95 (0.82, 1.10)	1.22 (0.94, 1.59)	0.32	
Family history of diabetes						
No	1.00	1.10 (1.02, 1.17)	0.94 (0.79, 1.11)	1.20 (0.88, 1.65)	0.26	0.68
Yes	1.00	1.05 (0.97, 1.13)	1.03 (0.87, 1.22)	1.28 (0.96, 1.69)	0.09	
History of hypertension						
No	1.00	1.05 (0.96, 1.15)	1.03 (0.83, 1.29)	1.39 (0.95, 2.04)	0.11	0.54
Yes	1.00	1.08 (1.02, 1.15)	0.96 (0.83, 1.10)	1.20 (0.93, 1.54)	0.18	

* Multivariable models were adjusted for age, ethnicity, BMI, physical activity, total energy intake, alcohol intake, smoking, menopausal status, postmenopausal hormone use and family history of diabetes.

Hazard ratios and 95% CIs of diabetes risk according to the number of cutaneous nevi in subgroup analyses stratified by predetermined factors among participants in the Health Professionals Follow-up Study*

Table 4

Subgroup	Number of cutaneous nevi				P trend	P for interaction
	0	1–5	6–14	15		
Age						
< 65 years	1.00	1.10 (0.96, 1.27)	1.18 (0.88, 1.59)	1.77 (1.13, 2.77)	0.01	0.46
65 years	1.00	0.95 (0.82, 1.09)	0.98 (0.72, 1.33)	1.50 (0.98, 2.30)	0.32	
Multivitamin use						
Current	1.00	1.08 (0.95, 1.23)	0.94 (0.70, 1.26)	1.46 (0.95, 2.24)	0.21	0.52
Never	1.00	0.99 (0.82, 1.20)	1.06 (0.70, 1.61)	1.65 (0.95, 2.87)	0.16	
Past	1.00	0.83 (0.62, 1.10)	1.73 (1.05, 2.86)	1.65 (0.69, 3.93)	0.10	
Smoking status						
Never	1.00	1.04 (0.89, 1.22)	1.06 (0.73, 1.53)	2.04 (1.16, 3.59)	0.06	0.87
Past	1.00	1.06 (0.92, 1.22)	1.03 (0.74, 1.41)	1.56 (1.02, 2.39)	0.08	
Current	1.00	1.10 (0.71, 1.75)	1.40 (0.59, 3.35)	0.54 (0.07, 4.30)	0.89	
BMI, kg/m ²						
Normal weight	1.00	1.08 (0.85, 1.36)	1.58 (1.02, 2.46)	2.57 (1.26, 5.27)	0.002	0.29
Overweight	1.00	1.02 (0.88, 1.17)	0.88 (0.62, 1.24)	1.63 (1.05, 2.53)	0.25	
Obese	1.00	1.03 (0.87, 1.22)	1.09 (0.77, 1.54)	1.85 (0.67, 2.10)	0.44	
Alcohol						
Never/rarely	1.00	0.97 (0.79, 1.18)	0.94 (0.62, 1.43)	0.86 (0.40, 1.85)	0.60	0.15
At least once a month	1.00	1.04 (0.93, 1.17)	1.14 (0.89, 1.46)	1.87 (1.32, 2.64)	0.001	
Physical activity						
1000 kcal/week	1.00	1.10 (0.93, 1.31)	1.16 (0.81, 1.66)	0.84 (0.41, 1.70)	0.67	0.03

Subgroup	Number of cutaneous nevi				P trend	P for interaction
	0	1-5	6-14	15		
>1000 kcal/week	1.00	1.00 (0.88, 1.12)	1.04 (0.79, 1.35)	2.05 (1.45, 2.89)	0.004	
History of hypercholesterolaemia						
No	1.00	1.05 (0.90, 1.22)	1.03 (0.72, 1.45)	1.92 (1.24, 2.99)	0.02	0.49
Yes	1.00	1.00 (0.88, 1.15)	1.14 (0.87, 1.49)	1.32 (0.85, 2.04)	0.17	
Family history of diabetes						
No	1.00	1.01 (0.89, 1.15)	1.09 (0.83, 1.42)	1.81 (1.24, 2.64)	0.01	0.55
Yes	1.00	1.02 (0.87, 1.19)	1.03 (0.72, 1.47)	1.13 (0.65, 1.98)	0.64	
History of hypertension						
No	1.00	1.05 (0.90, 1.22)	1.06 (0.76, 1.49)	1.63 (1.01, 2.62)	0.08	0.92
Yes	1.00	1.00 (0.88, 1.14)	1.08 (0.82, 1.42)	1.42 (0.94, 2.14)	0.15	

* Multivariable models were adjusted for age, ethnicity, BMI, physical activity, total energy intake, alcohol intake, smoking and family history of diabetes.